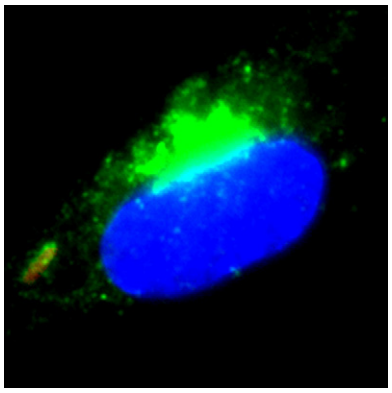
Microbiology Select

Cell

Pathogens and their hosts have been in an evolutionary arms race for millions of years, and much has been learned about the strategies each has developed to stay on top. This Select focuses on recent papers reporting new insights into the mechanisms used by pathogens to stay in the race, either by hijacking host proteins and cellular pathways or, in one case, by hitching a ride on an insect vector to move from host to host.

Opening the Lid for *Legionella*



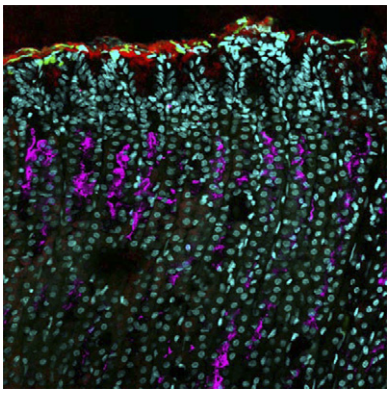
Mouse macrophage infected with wild-type *Legionella* (red) shows Rab1 (green) staining of preinuclear Golgi and of the *Legionella* vacuole. Image courtesy of A. Ingmundson.

Legionella pneumophila, the bacterium that causes Legionnaires' pneumonia, is taken up by alveolar macrophages after being inhaled. *L. pneumonia* bypasses the macrophage's lysosomal network and replicates in an intracellular vacuole that recruits vesicles from the host cell's endoplasmic reticulum (ER). Vesicle recruitment depends on the bacterial proteins SidM/DrrA and LidA, which target the host's small GTPase Rab1 to the vacuole. Rab1 is an important regulator of ER to Golgi vesicle transport. Two recent studies (Ingmundson et al., 2007; Machner and Isberg, 2007) now report that the SidM/DrrA exerts a dual function to take control of the host cell's Rab1. First, SidM/DrrA displaces the Rab1 inhibitor GDI (guanine nucleotide dissociation inhibitor) and then acts as a GDP/GTP exchange factor (GEF) for Rab1. SidM/DrrA therefore encompasses both activities that are required for Rab1 activation. SidM/DrrA also recruits Rab1 to the membrane of the *Legionella* vacuole. Machner and Isberg provide evidence that the GDI dissociation induced by SidM/DrrA is a prerequisite for LidA to bind to Rab1. They find that LidA is unable to recruit Rab1 to the *Legionella* vacuole in the absence of SidM/DrrA's GDI displacement activity, implying that the two bacterial proteins act in sequence. Meanwhile, Ingmundson et al. identify another *Legionella* protein LepB as a downstream effector of Rab1. The authors find that LepB acts as a Rab1 GTPase-activating protein (GAP) and is associated with late *Legionella* vacuoles, which have recruited ER vesicles. They propose that SidM/DrrA first causes Rab1 activation and recruitment to the pathogen vacuole where Rab1 then mediates fusion of ER vesicles with the vacuole. In late vacuoles, SidM/DrrA disappears from the membrane and LepB could inactivate Rab1 by stimulating its GTPase activity, which coincides with the dissociation of Rab1 from the membrane. The two papers provide evidence that a certain order of events is crucial during early stages of infection with *Legionella*, suggesting that therapeutic interference with these steps might provide an opportunity to stop this deadly infection in its earliest stages.

A. Ingmundson et al. (2007). Nature. Published online October 21, 2007. 10.1038/nature.06336.
M.P. Machner and R.R. Isberg (2007). Science. Published online October 18, 2007. 10.1126/science.1149121.

How *H. pylori* Hangs on Long-Term

Although infection with a pathogen may lead to the host's demise, there are many examples of chronic infections where the pathogen establishes its presence in the host without killing it. One example of a bacterial pathogen that can cause long-term infection is *Helicobacter pylori*, which colonizes the gut and if the infection is not treated can persist for decades. Symptoms range from chronic active gastritis without clinical symptoms to severe ulceration and eventually development of stomach cancer. The outcome of the infection is the result of the complex interplay between the host and the bacterium. Several bacterial proteins, such as CagA, are known to play an important role during infection. It is thought that by triggering apoptosis of gut epithelial cells they are responsible for the more acute form of the disease. The CagA protein has also been shown to interact with many host proteins, such as members of the GRB2/CRK/MEK signaling pathway. But how does the microbe establish and maintain a chronic infection, given that the gut cells have a naturally high turnover rate and the bacteria are shed together with the cells? Mimuro et al. (2007) now report the unexpected finding that *H. pylori* infection protects gut cells from undergoing apoptosis. Using a rodent model of *H. pylori* infection, they find that CagA stimulates the expression of the host survival protein MCL1 by activating the GRB2/MEK/ERK signaling pathway in the infected cell. MCL1 inhibits the activation of intrinsic proapoptotic factors such that *H. pylori* infection protects against intrinsic,



Immunohistochemical staining of gastric tissue infected with CagA mutant H. pylori treated with a proapoptotic agent. Apoptotic cells (green) are localized in the pits (red) with exfoliation of mucosal layers. Neck cells (pink) and DNA (blue) are also shown. Image courtesy of H. Mimuro.

but not extrinsic, apoptotic stimuli. The authors propose that the CagA protein helps *H. pylori* to occupy the gut microenvironment long-term. The finding that *H. pylori* inhibits cell-intrinsic apoptosis raises the interesting possibility that this pathogen-induced survival signal might be the trigger for tumorigenesis, potentially contributing to the development of gastric carcinomas associated with *H. pylori* infection.
H. Mimuro et al. (2007). Cell Host & Microbe ***2****, 250–263.*

A Trojan Horse Conquers a Plant Cell Nucleus

The soil bacterium *Agrobacterium tumefaciens* reprograms infected host plant tissue by transfecting and integrating a plasmid-derived T-DNA into the plant genome. The T-DNA is transported into the nucleus with the help of the bacterial proteins VirD2 and VirE2 and a plant cell protein, VIP1, which binds to VirE2. However, the role of the host VIP1 protein in this process has been unclear. Djamei et al. (2007) now reveal an elegant mechanism by which *A. tumefaciens* takes advantage of the host's pathogen response (PR) system. Upon infection with the pathogen, plant cell mitogen-activated protein kinases (MAPKs) are activated resulting in expression of PR genes. The authors show that VIP1 is a transcription factor that induces expression of PR genes and is itself a direct target of a plant MAPK called MPK3. Phosphorylation of VIP1 by MPK3 enables VIP1 to move to the nucleus, allowing the VirE2/T-DNA complex to hitch a ride to the nucleus as well. Therefore, *A. tumefaciens* is able to hijack the plant's defense signaling system to organize a ride for its T-DNA to the host cell nucleus. This raises the interesting question of whether this "Trojan horse" mechanism is exploited by other plant or animal pathogens.
A. Djamei et al. (2007). Science ***318****, 453–456.*

Plant Virions Hail a Cab

CaMV protein P2 (in green) binds exclusively at the extreme tip of the vector aphid maxillary stylet. Image courtesy of M. Uzest.

Many pathogens not only exploit their host's cellular environment but also take advantage of non-host organisms, such as insect vectors, in a strategy to overcome their immobility and to spread to new hosts. Sap-sucking insects like aphids serve as vectors for many plant viruses, but little is known about the cellular or molecular interactions of viral pathogens with insect vectors. Uzest et al. (2007) now provide evidence that the cauliflower mosaic virus (CaMV) binds to a receptor found in the mouthparts of its aphid vector. Analysis of the vector mouthparts by electron microscopy led to identification of a specific anatomical region at the extreme tip of the maxillary stylets that contains virion particles. Using an in vitro system with isolated stylets, the authors show that the virus protein P2, which is known to establish a link between the virus and the vector, is located at the very tip of the insect's maxillary stylets. CaMV virions with a mutant P2 protein show decreased binding to stylets and are not transmitted from plant to plant by aphid vectors. The authors also report that wild-type P2 is unable to bind to the stylets of nonvector aphids, suggesting that a functional P2 protein is essential for virions to bind to vector aphid stylets and that there must be a specific receptor for P2 in the stylets of these insects. The authors surmise that the receptor for P2 is an insect protein deeply embedded in the chitin matrix of the stylet. It will be interesting to discover the molecular identity of this receptor and to find out whether this receptor is also used by other plant viruses. This may pave the way to designing interventions that will put a stop to the viruses' ability to move from plant to plant via its aphid taxi service.
M. Uzest et al. (2007). Proc. Natl. Acad. Sci. USA. Published online October 25, 2007. 10.1073_pnas.0706608104.

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